We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

7

Schistosomasis and Bladder Cancer

Saad S. Eissa, M. Nabil El-Bolkainy and Mohab S. Eissa
Department of pathology, National Cancer Institute, Cairo University
Egypt

1. Introduction

Schistosomiasis also known as *Bilharziasis*, is a parasitic disease that dates back to antiquity. The ancient Egyptians, through settling and cultivating the Nile valley, were among the first to contract the disease. Thus, the main symptom hematuria was mentioned in Egyptian papyri (1500-1800 B.C.), and schistosome eggs were identified in Egyptian mummies through paleopathologic studies. In 1852, Theodor Bilharz, a German pathologist working in Cairo, discovered the worms in the portal circulation and was the first to describe the Pathology of the disease. Ferguson in 1911 was the first to report on the high frequency of bladder cancer in Egypt and to suggest an etiologic relation with urinary *Schistosomiasis*, a fact which is now generally accepted (Bolkainy & Chu 1981a). The aim of this article is to review the pathobiology of *Schistosoma* associated bladder cancer (SACB), describe the relationship between *Schistiosomiasis* and bladder cancer with respect to the mechanisms of carcinogenesis with emphasis on special features of SABC and recent methods of early detection.

2. Incidence and risk factors

An estimated 386,300 new cases and 150,200 deaths from bladder cancer occurred in 2008 worldwide (Jemal et al.,2011). The majority of bladder cancer occurs in males and there is a 14-fold variation in incidence internationally. The highest incidence rates are found in the countries of Europe, North America, and Northern Africa. Egyptian males have the highest mortality rates (16.3 per 100,000), which is twice as high as the highest rates in Europe (8.3 in Spain and 8.0 in Poland) and over 4 times higher than that in the United States (Ferlay et al., 2010) Smoking and occupational exposures are the major risk factors in Western countries, whereas chronic infection with *Schistosoma hematobium* in developing countries, particularly in Africa and the Middle East, accounts for about 50% of the total burden.(Parkin,2006) A majority of bladder cancers associated with *schistosomiasis* are squamous cell carcinoma, (SCC) while those associated with smoking are transitional cell carcinoma (TCC) (Sliverman et al.,2006).In the United States, mortality rates have stabilized in males and decreased in females from 1997 through 2006, (Edwards et al.2010) and in Europe declines have been observed in most countries since the 1990s, (Karim-Kos et al.,2008) due in part to reductions in smoking prevalence and reductions in occupational exposures known to cause bladder cancer. Bladder cancer continues to be the most common cancer among males in Egypt (Ferlay et al.2010), despite the large decreases in schistosomiasis.This is likely the result of a reduction in *schistosoma*-related bladder cancers being offset by an increase in tobacco-

related bladder cancers.(Althuis et al., 2005). The association with *Schistosomiasis* determines a distinct clinico-pathologic entity quite different from that experienced in the Western world. It is commonly a well-differentiated SCC (80 %) with a limited tendency to lymphatic and blood stream metastasis despite the locally advanced stage of tumors in the majority of patients. Compared with Western series the tumors are multiple in 22% of cases and are frequently associated with atypical epithelial changes in the rest of the urothelium. SABC was encountered at an earlier age in patients with schistosome eggs in the specimens. About 95% of cases are muscle invasive at the time of presentation and, in absence of effective systemic therapy, these cases are often fatal. In fact, until recently, SABC has been the most common cause of death among men age 20– 44 years (Freedman et al.,2006). *Schistosomiasis,* is now a widespread endemic disease currently found in 75 countries. In the Nile Delta area, mixed infection with S. haematobium and *S. mansoni* is endemic, while *S. haematobium* is more prevalent in Upper Egypt due to the greater abundance of the specific intermediate host snails in that area. In s*chistosomiasis* due to *S. haematobium*, the intensity of infection is correlated with morbidity, the degree of hematuria and proteinuria, and the pathological changes observed in the urinary bladder and ureters and malignancies of the bladder. The evidence associating *S. haematobium* infection with the development of bladder cancer is, however, far greater than that for any other parasitic infection; it has been supported by several major studies in countries in Africa and the Middle East (Moustafa et al.,1999). Cigarette smoking is now recognized as a major cause of bladder cancer in developed countries, increasing the risk two to three fold in North America and Europe and accounting for 50% of these cancers in males and 25% in females. Although much less information is available from developing countries, a recent study in Egypt indicated that smoking was strongly associated with bladder cancer in males and could account, at least in part, for 75% of these cancers (Freedman et al.,2006). Other risk factors **i**ncludes certain organic chemicals – particularly aromatic (aryl)-amines such as naphthalene, benzidine, aniline dyes, and 4-aminobiphenyl – are known bladder carcinogens and have helped identify high-risk occupations, including petroleum chemical/rubber workers, hairdressers, painters, textile workers, truck drivers, and aluminum electroplaters. Bladder cancer may also result from pelvic radiotherapy, phenacetin use, and cyclophosphamide exposure, resulting in a four- to five-fold relative risk increase, particularly when exposure is in a chronic low-dose form *(*Ibrahim & Khaled,2006*).*

3. Evidence supporting the relationship between schistosomiasis and bladder cancer

3.1 Epidemiological evidence

The association of bladder cancer with *schistosomiasis* seems to be related to the endemicity of the parasite. Urinary *Schistosomiasis* is endemic throughout most of Africa, the Middle East, Madagascar, Reunion, Mauritius and India. In Africa, a high frequency is reported in countries along river Nile such as Egypt and Sudan, as well as, countries around lake Victoria as Kenya and Uganda. The disease is also prevalent in the west of the continent (Gold Coast and Senegal) and the eastern side of the continent below the Equator (Mozambique, Zambia and New Guinea) (Moustafa,et al.,1999). In the Middle East, it occurs in Iraq, Iran, Syria, Saudi Arabia and Yemen (Al-Saleem et al.,1990, Al-Shukri et al.,1987, Elem, & Purohit,1983).The consensus of available information strongly implicates an association between *S. haematobium* infection and the induction of bladder cancer. In Egypt,

bladder cancer has been the most common cancer during the past 50 years. In 2002, Egypt's World-standardized bladder cancer incidence was 37/ 100,000, representing approximately 30,000 new cases each year(Parkin et al.,2005). Interestingly, the most common histopathological type of bladder cancer in Egypt has been SCC, constituting from 59% to 81% of reported bladder cancers between 1960 and 1980 (El-Mawla et al.,2001). Contrary to the leading etiology of smoking and occupational exposures in Western countries, chronic bladder infection with *Schistosoma haematobium*, the nematode causing urinary schistosomiasis, has been the most important risk factor for bladder cancer in Egypt (Moustafa et al.1999) This neoplasm accounts for 30.8% of the total cancer incidence and is ranked first among all types of cancer recorded in Egyptian males and second only to breast cancer in females (Mokhar et al.,2007). Changes in exposures linked to bladder cancer have occurred recently in Egypt. Prior to the 1964 completion of the Aswan High Dam, approximately 60%of people in North and South Egypt were infected with S. haematobium; a similar proportion was infected with *S. mansoni* (causing intestinal disease) in North Egypt, but rarely seen in southern parts of the country(El-Khoby et al.,2000). The dam appears to be responsible for a gradual replacement of *S. haematobium* by *S. mansoni* in North Egypt, and *S. mansoni* has expanded into southern regions (Felix et al.,2008). Another change in bladder cancer risk involves rising cigarette smoking in Egypt, which is now 32% among males (but only 7% among females) (WHO, 2000). In other countries, such as Iraq, Malawi, Zambia and Kuwait, where the endemicity of *schistosomiasis* due to either mixed or *S. haematobium* infestations is high, bladder cancer was also reported to be the leading cancer (Felix et al.,2008). In contrast, in *schistosome*-free countries bladder carcinoma ranks from the 5th to the 7th most common cancer in men and from the 7th to the 14th in women (Moustafa et al. 1999). With the reduction in *schistosomiasis* due to control efforts over the past 30–40 years, the epidemiology of bladder cancer in Egypt has shifted dramatically. This is exemplified by a recent study from Gouda et al (2007) in which they reviewed 9843 patients treated for bladder cancer by Egypt's National Cancer Institute (NCI) in Cairo between 1970 and 2007. The authors identified a dramatic decline in the proportion of patients with bladder cancer who had *schistosoma* ova on pathological evaluation (82.4% vs 55.3%) and in the proportion of patients treated for bladder cancer (from 27.6% of patients treated for cancer to 11.7%). They also describe an increase in the median age at presentation (from 47.4 years to 60.5 years), a decrease in the male to female ratio (from 5.4 to 3.3) and a decrease in the proportion of patients with SCC histology (from 75.9% to 33.0%). A similarly designed study from the Egyptian NCI in Cairo showed that patients treated for bladder cancer in 2005 had a six-fold increased risk of TCC of the bladder (vs SCC) compared with patients treated in 1980 (Felix et al.,2008) They also evaluated the incidence of SABC at several other institutions in Egypt during this period and showed no rise in incidence at other institutions as the incidence decreased at the NCI. Furthermore, these epidemiological trends have also been documented in the Egyptian nation-wide tumor registries (Salem et al., 2000, Freedman et al., 2006). The increase in frequency of TCC and decrease in frequency of SCC relative to previous reports indicate a transition phase from the SABC to the Western type of bladder cancer related to smoking, exposure to occupational and agricultural related chemicals. (Ibrahim & Khaled, 2006)

3.2 Experimentally induced schistiosomiasis

Several attempts were made to evaluate the carcinogenic potential of experimentally induced schistosomiasis. It has been suggested that chronic tissue injury could provide a

promoting factor which acts to increase the rate of cell turnover via the induction of restorative hyperplasia and squamous metaplasia. Most of this focal hyperplasia is subsequently reversible However, in some situations, hyperplasia and dysplasia may become irreversible, particularly during concomitant exposure to low (sub-carcinogenic) doses of carcinogens e.g., N-nitroso compounds (Hicks,.et al., 1980).

3.2.1 Inflammatory cells

Schistosomiasis induces chronic irritation and inflammation in the urinary bladder, and this could facilitate changes in at least two stages of the development of the disease: first, initiation of premalignant lesions, and second, action as a promoting agent to increase the likelihood of the conversion of these lesions to the malignant state. At the stage of initiation, activated macrophages induced at the sites of inflammation are implicated in the generation of carcinogenic N-nitrosamines (NNA)and reactive oxygen radicals (Moustafa et al., 1994) that lead to DNA damage and subsequently to events such as mutations, DNA strand breaks, and sister chromatid exchanges. Inflammatory cells have also been shown to participate in the activation of other bladder carcinogens such as the aromatic amines (Badawi et al., 1992, 1995a).

3.2.2 Bacterial infections

Various species of bacteria including nitrate –reducing bacteria have been found in greater numbers in the urine of patients with *schistosomiasis* than in the urine of uninfected patients (Mostafa et al.1994). These higher levels of infection probably result from the tissue damage caused in various parts of the urinary tract by the egg-laying activities of the worms (Lehman et al.,1973, Falagas et al.2010). Injury to the urothelium from the passing eggs and/or bacterial infection might decrease the effectiveness of the mucosal barrier to reabsorb carcinogens in urine. Several of these bacterial species can mediate the N-nitrosation of amines, thereby providing a source of carcinogenic NNA in addition to those from exogenous sources (EL-Merzabani et al.,1979, Moustafa 1999).

3.2.3 N-Nitrosamines

Attention has focused on nitrite and N-nitroso compounds (NNCs).(Badawi et al.1995a) NNCs can be formed endogenously following the secondary infection by nitrate-reducing bacteria that invariably accompany schistosomal cystitis. NNCs, including nitrosamines and the direct-acting nitrosamides, are carcinogenic, inducing tumorigenic alkylation of specific bases and DNA sequences(O'Brien et al., 1988, Badawi et al.,1993,1994). Evidence of the interaction of carcinogens, with the genetic material of the bladder has been obtained by analyzing bladder mucosal DNA for the presence of mutations (Marletta,1988,Badawi et al.,1995b). Mutations have been observed in oncogenes, tumor suppressor genes, and genes associated with cell cycle control. In particular, mutations in the tumor suppressor gene p53 have been observed more frequently in patients with SABC than in patients with non-SABC(Badawi 1996). Changes in these and other genes and in microsatellite DNA, presumably arising as a result of carcinogenic insults, may lead to greater genetic instability and hence to the malignant transformation (Yamamoto, et al., 1997). Genomic DNA hypomethylation has been recently suggested as biomarker for to identify individuals who are more susceptible to the development of bladder cancer (Theodorescu 2003) Moreover, Inflammatory cells also participate in the activation of procarcinogens, such as aromatic amines and polycyclic

aromatic hydrocarbons, to their ultimate carcinogenic metabolites (i.e., the final reactive form of the carcinogen) (Badawi et al.,1993). Since the aromatic amines are an important group of bladder carcinogens, an increased number of inflammatory cells in the urinary bladder of *schistosomal* patients may enhance the carcinogenic potential of these agents by increasing their rate of activation (Moustafa et al., 1994).

3.2.4 Cigarette smoking

Tobacco use is a well-documented risk factor for developing bladder cancer, but specific carcinogen(s) and molecular pathway(s) have not been elucidated. Much interest has focused on aromatic amines such as 4-aminobiphenyl (ABP) because they are found not only in cigarette smoke but also in several industrial chemicals. One potential mechanism by which amines cause carcinogenesis is by forming DNA adducts that result in transitional mutations(Kadlubar & Badawi 1995, Kaderlik, & Kadlubar 1995,). Habuchi et al., 1993 suggested that cigarette smoking might have a significant impact on the mutations of the p53 gene in urothelial cancers. Urothelial carcinogenesis in the presence of schistosomiasis seems to proceed along pathways different from those linked to smoking, since cigarette smoking appears to have a significant impact on the mutation of the p53 gene with A:T to G:C transitions which are not observed in SABC (Habuchi et al., 1993). The association of human papilloma virus (HPV) and non-schistosomal bladder squamous cell cancers has been reported in isolated cases in the USA (Maloney et al., 1994). An Egyptian study has also demonstrated HPV DNA in six of 16 (38%) SABC (Zekri et al.,1995). While SABC in South Africa showed no associated HPV (Cooper et al.,1997).

3.2.5 Occupational exposure

Exposure to chemicals used in dye, rubber, and textile manufacturing have been estimated to be responsible for up to 20% of bladder cancer cases (Cole et al.,1972). Most of these chemicals are aromatic amines that take several years to accumulate and thus account for the long latent periods before the development of bladder cancer. Aromatic amines from occupational exposures are activated and detoxified through the same reactions that aromatic amines in cigarette smoke are activated and detoxified. Hence, bladder cancer susceptibility depends on the cumulative expression profiles of these activating and detoxifying enzymes. It also means that exposures to occupational agents and cigarette smoke may be additive (Jung & Messing, 2000).

3.3 Genetic changes

The major differences in the clinico-pathologic features observed between the Western type of bladder cancer and SABC probably reflect underlying alternate tumor biology and carcinogenic pathways. Several studies attempted to characterize the chromosomal aberrations of SABC, including both SCC and TCC subtypes. Data were compared with those of the Western world.

3.3.1 Chromosomal studies

Over representation of 5p,6p,7p,8q,11q,17q and 22q of chromosomal material has been detected by Cytogenetic and molecular analysis. Aberrations of chromosomes 7, 9, and 17 showed reciprocal patterns in TCC and SCC, whether associated with Schistiosomiasis or not (Pycha et al. 1998). Few sporadic SCC cases examined by comparative genomic

hybridization (CGH) have shown gains at 1q, 8qa, and 20q, as well as loses of 3p,9p, and 13q (El-Rifai et al.2000). Changes were observed at similar frequencies in SCC and TCC, irrespective to schistosomal status suggesting that these changes may be involved in a common pathway for bladder cancer development and progression independent of schistosomal status or histological subtype (Badawi,1996).

3.3.2 Cancer genes

Currently, it would appear that chromosome 9 and P53 changes may occur relatively early in the genesis of bladder cancer (Simoneau et al., 1996 , Reznikoff et al., 1996). The retinoblastoma (Rb) gene on chromosome 13 (13q) and the p53 gene on chromosome 17 (17p) play an important role in the progression of bladder cancer and possibly its development (Esrig et al., 1994). Rb gene mutations are seen in approximately 30% of bladder cancer (Cordon cardo et al.,1992). Inability to detect pRb immunohistochemically is associated with increased tumor grade and stage, especially muscle invasion (Xu et. al.,1993, Grossman et al.,1993) Some Studies revealed that Allelic losses in chromosome 17p, where the p53 gene resides, were less frequent in SCC (38%) than TCC (60%) Gonzalez-Zulueta,1995 while in South Africa, p53 mutations were recorded in 57% of SABC. (Badawi et al. 1999). It was also demonstrated that the histopathological subtype rather than the schistosomal impact itself determines the pattern of chromosomal changes for SABC. The pattern of point mutations in p53 appears to reflect the site of tumor origin, with most of the transitions occur in mutational hot spots at CpG dinucleotides (Hollstein et al., 1991). TP53 mutations in SABC included more base transition at CpG dinucleotids than seen in urothelial TCC. p53 inactivation ranged from 0 to 38% at the early stage of the disease, as opposed to 33% to 86% in the advanced tumor stage (Weintraub et al.1995, Badawi et al. 1996,) Excess mutations might be due to high levels of urinary nitrates in Schistoma infected patients producing nitric oxide by inflammatory cells. In these cases, there is usually an overexpression of MDM2 as well (Osman et al.1997). Elevated levels of DNA alkylation damage have been detected in *schistosome*-infected bladders and are accompanied by an inefficient capacity of DNA repair mechanisms. Whereas the p53 mutation frequency in SCC was similar to that reported for invasive TCC, there were differences in the type and position of these mutations between the two tumor types (Gonzalez-Zulueta et al., 1995). The ras oncogene does not seem to be strongly implicated in the differential process of carcinogenesis in SABC, judging from studies in different countries (Czerniak et al., 1990, Ibrahim & Khaled,2006). Deletions on chromosome 9 not only appear to occur in > 60% of bladder cancer across all grades and stages, but also are likely an initiating event (Jung & messing 2000). The p21 region of chromosome 9 (9p21) has been found to be mutated in a variety of malignancies suggesting the presence of a common tumor suppressor gene.(Theodorescu, 2003). Tamimi et al.(1996) found that a $p16^{INK4}$ deletion was present in 23 of 47 samples from SABC patients and that mutations were present in another 2 patients (i.e; 53% of tumors exhibited $p16^{INK4}$ gene alterations). They concluded that $p16^{INK4}$ alterations are more frequent in SABC than in other bladder tumors and may thus be associated with a specific etiology.

3.3.3 Microsatellite Instability

Microsatellite abnormalities found in cancer bladder appear to be early changes (Linnenbach et al., 1994; Orlow et al., 1994, Gonzalez-Zulueta et al., 1995), they may be reflecting severe deregulation of cellular DNA which if left unchecked may lead to

unrepaired mutations in key regulatory genes such as p53. Importantly, microsatellite alterations are common in bladder cancer and analysis of genomic instabilities in urine samples has been recently evaluated as a method for bladder cancer screening with promising results in terms of sensitivity, specificity compared to classical techniques (Seripa et al., 2001; Zhang et al., 2001; Berger et al., 2002; Utting et al., 2002).

3.3.4 Oncogenes

Oncogenes may contribute to transformation and progression by being either overexpressed or mutated to produce an oncoprotein. One of the more important mechanisms by which oncogenes are overexpressed in bladder Cancer is through gene amplification (increased copies of the gene). In small series of SABC HER-2/ neu was overexpressed in all the studied TCC and none of SCC studied by Immunohistochemistry (Coombs et al., 1991, Cote et al.,1998, Wishahi,.et al.2000).

3.4 Cancer progression

Bladder Cancer cells require the acquisition of certain properties prior to being able to grow rapidly, invades, and metastasizes. These properties include uncontrolled growth and cellular mobility, mediated at least in part via EGF and EGFRs, expression or loss of expression of specific cell adhesion molecules, and overproduction of angiogenic factors. These factors may be produced by the tumor cells or released by the surrounding extracellular matrix or tumor associated stromal cells, or they may be products of inflammatory cells that infiltrate tumors. Folkman et al., (1987) using immunohistochemistry, increased microvascular density as a surrogate for angiogenesis has been found to be associated with tumor progression and decreased overall survival in Bladder Cancer patients.(Bochner et al.1995). The association of the apoptosis related proteins Bcl-2, Bcl-x, Bax and Bak, p53, E-cadherin, epidermal growth factor receptor and c-erbB-2, OCNA and Ki-67 were correlated with the clinical outcome of SACB in Cystectomy specimens from 109 patients with organ confined, muscle invasive stage, pT2pN0M0 were studied by Haitel and coworkers (2001) Immunohistochemical results were correlated with tumor progression. On multivariate analysis p53 emerged as a significant prognostic factor Additional independent prognostic factors were proliferating cell nuclear antigen for squamous cell carcinoma, and MIB-1, Bcl-x and Bax for transitional cell carcinoma.

4. Age and gender ratios

In *schistosome*-free countries throughout the world, the peak incidence of bladder cancer is in the sixth or seventh decade of life (La Vecchia et al., 1991) and is maximal between the ages of 65 and 75 years). Only 12% of bladder cancer cases occur in people younger than 50 years(Burnham, 1989). By contrast, in Egypt, Sudan, Iraq, Zambia, Malawi, and Zimbabwe, the mean age of the highest incidence of SABC is between 40 and 49 years (Moustafa et al., 1999), which clearly contrasts with the findings for *non-schistosoma* areas. The ratio of bladder cancer incidence (males to females) in countries with endemic infection was reported to be 5:1 but may vary within the range of 4:1 to 5.9:1 (Ibrahim,1986). The relatively higher gender ratio in the countries with endemic infection has been suggested to be because in rural areas the main route for infection is through contact with infected waters during agricultural activities, which are normally done by men rather than women. The predominantly male development of SABC has been explained by the high frequency of loss

of chromosome Y using the FISH technique. Khaled et al.,(2000) demonstrated that 41% of cases of SABC showed loss of chromosome Y.

5. Pathobiology of schistosoma associated bladder cancer

SABC is histopathologically distinct from *non-S. haematobium* associated bladder cancer that occurs in North America and Europe. The former cancer is usually, sparing the bladder's trigone. Although the majority of bladder tumors formed due to *Schistosoma* infection are squamous cell carcinomas (SCC), adenocarcinomas and transitional cell carcinomas (TCC) or undifferentiated carcinomas can develop (Johansson & Cohen, 1997) Furthermore, it appears that there is a proportional increase of TCC due to schistosomal infections over time (Koraitim et al.,1995). Some researchers believe that TCC need more time to progress than SCC and are closely related with a less devastating inflammatory infiltrate (Michaud et al., 2007).

5.1 Gross features

The tumors commonly appeared as large nodular masses (Figure. 1) whereas papillary types are rare (2%). The carcinoma usually arises from the upper vesical hemisphere, at the posterior wall or vault. The trigone is rarely the site of the tumor origin (2%) (Khafagy et al.,1972) in contradistinction to the *non-shistosoma* associated cancer bladder where it involved in 21% (Mostofi,1975).

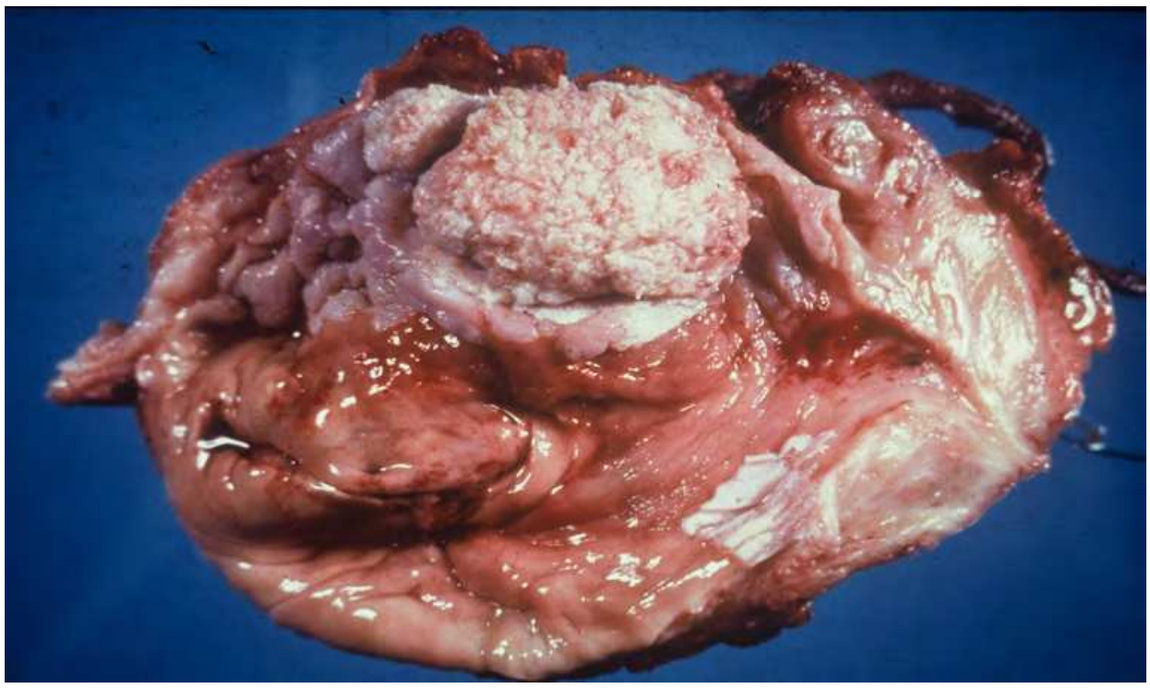


Fig. 1. SABC nodular type associated with leucoplakia

5.2 Precursor lesions

In the *Schistosoma* infested urinary bladder, the urothelium usually undergoes various metaplastic, proliferative and atypical changes (Khafagy et al., 1972). Metaplasia refers to a

change in cell type, and this explains the histogenesis of non-transitional tumors in the bladder. Thus SCC and adenocarcinoma arise on top of squamous metaplasia and columnar metaplasia respectively. It is important to distinguish simple hyperplasia of the urothelium from atypical lesions (dysplasia and carcinoma insitu). The former is a simple reversible change, but the latter are associated with an increased risk of neoplastic development. Dysplasia, or low grade intraurothelial neoplasia, referred to pre-neoplastic atypical epithelial changes short of frank malignancy. Conversely, carcinoma insitu (CIS), or high grade intraurothelial neoplasia, is a preneoplastic atypical lesion which is cytologically

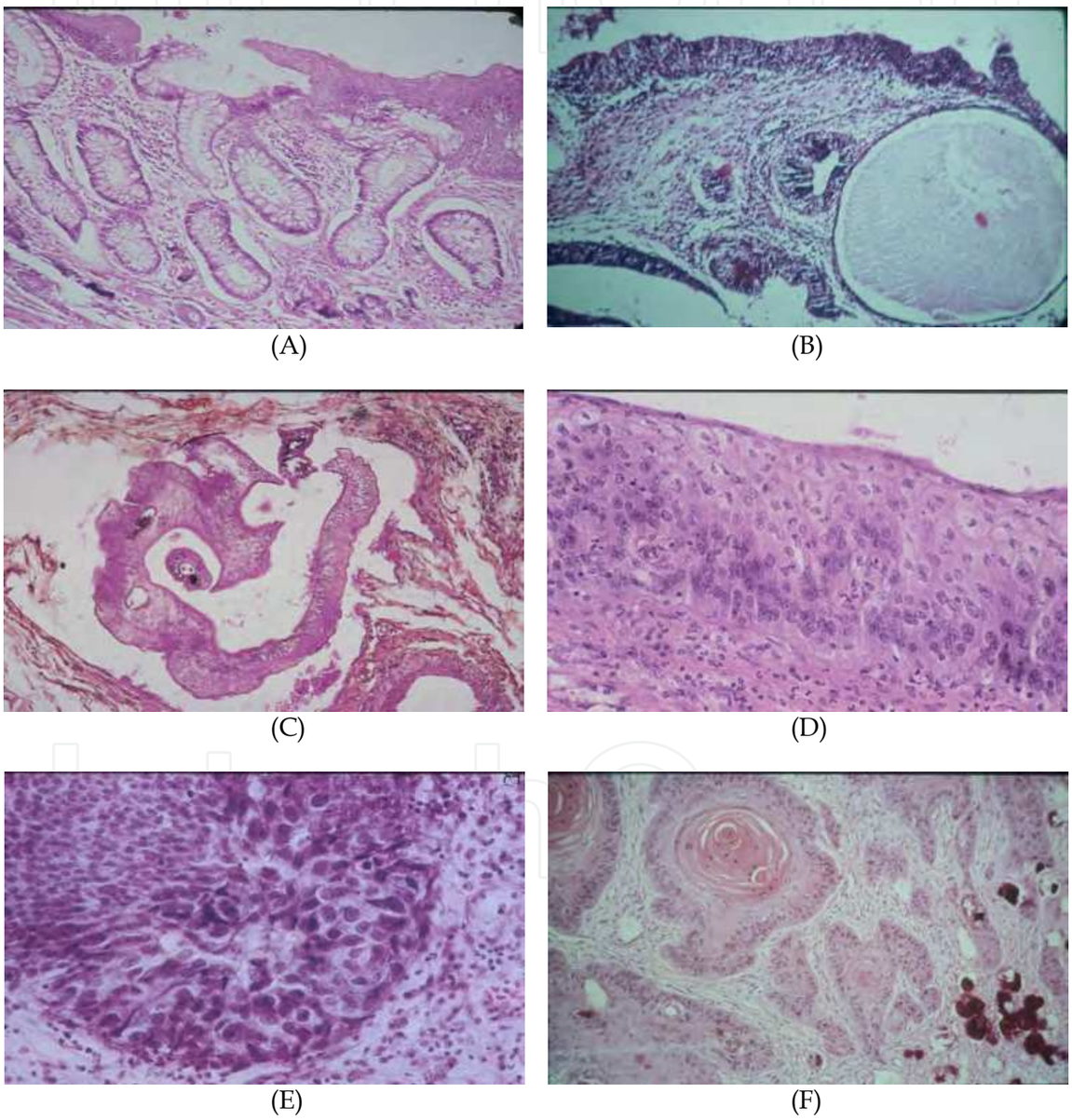


Fig. 2. A) Simple Squamous metaplasia. B) Cystitis glandularis & cystica. C) Schistosoma worm in a vein. D) Squamous dysplasia. E) CIS in Brunn's nest F) SAB- Squamous cell carcinoma grade I.

indistinguishable from invasive cancer, but without invasion of the basement membrane. The rate of progression to invasive cancer is 15 % in cases of dysplasia (Cheng et al., 2000) and 35 % in CIS (Cheng et al., 1999). The SABC is frequently associated with a variety of pathologic changes in the bladder mucosa including: leucoplakia, cystitis cystica, carcinoma in situ and different *schistosoma* lesions (Zahran et al., 1976). In a series of Khafagy et al., (1972) of SABC 26 % of cases showed squamous metaplasia, 53 % of these lesions were non-keratinizing and 29 % showed surface keratinization and 18 % showed basal cell hyperplasia and atypia (Figure. 2).

Columnar metaplasia in the form of Brunn's nests, cystitis glandularis and cystica was observed in 52%-63 % (Khafagy,et al., 1972 & Zahran et al., 1976) of cystectomy specimens. Cystitis glandularis with atypia has been described by El-Bolkainy & Chu (1981a) at the tumor margin of adenocarcinoma. The natural history of these proliferative lesions has not been adequately studied due to lack of prospective follow up evaluation. Some of these changes such as simple hyperplasia and non- keratinizing squamous metaplasia without atypia are probably benign, however there is considerable evidence that atypical forms especially keratinizing squamous metaplasia (leucoplakia) may in fact have a premalignant potential. Similar evolutions may be expected in simple and atypical lesions of transitional epithelium. (Weiner et al., 1997).

5.3 Tumor histologic types

The urothelium is a multipotential unstable epithelium hence the multiple tumor types which may arise from it.

5.3.1 Transitional cell Carcinoma

In the SABC, transitional cell carcinoma contributed about 25 % of cases in large series collected over several years (Ghoneim et al., 1997), but there has been an increase in its relative frequency in recent years (Table 1). Three histologic subtypes and 10 rare variants are recognized.

Years	(1976-1978)	(1991-1993)	(2000-2002)
No. of patients	1059	1256	923
Squamous carcinoma	78%	53%	40%
Transitional carcinoma	16%	36%	49%
Adenocarcinoma	4%	6%	5%
Undifferentiated	2%	5%	6%
Schistosoma ova	82%	59%	52%

Table 1. Time trend analysis of histologic types of bladder carcinomas in cystectomy specimens (Zaghloul et al., 2008).

5.3.2 Papillary transitional neoplasm of low malignant potential

This type is a papillary noninvasive tumor (Ta) which resembles a papilloma but with epithelial thickening exceeding the normal 6 layers. It contributes about 20% of all papillary tumors. Histologically, it shows preserved normal cell polarity with intact umbrella cells and intact basement membrane, no cellular atypia, and infrequent mitosis restricted to basal cell layer. Rarely may it show a prominent endophytic or inverted pattern. Such tumors were previously classified as grade I TCC. However, long term follow up studies have

confirmed its rather benign nature. Thus, whereas 52 % of cases recurred, only 2% progressed to muscle invasive, and hence are considered favorable tumors of borderline malignancy or very low malignant potential.

5.3.3 Papillary transitional carcinoma

This refers to papillary tumors, which are composed partially, or entirely of malignant transitional epithelium. This type may be invasive or noninvasive. It is usually exophytic in pattern, rarely endophytic. Histologically, it shows both architectural disorder, as well as, cellular atypia of variable degree. They are graded either on a scale of three or a scale of two (low and high grades).

5.3.4 Invasive transitional carcinoma

This describes a non-papillary urothelial carcinoma (Figure.3) that invades the bladder wall; hence an aggressive behavior is expected. Such invasive property may complicate a papillary tumor, or may arise de novo. Also, these tumors are graded either on a scale of 3, or a scale of 2 (low and high grades). For therapeutic and prognostic implications, it is important to describe the pattern of invasion at tumor margin, namely: expansile with broad-front or tentacular growth, as well as, the depth of invasion, namely: infiltration of lamina propria(focal or extensive) or muscularis propria. In SABC the majority of tumors are invasive and 86% are high grade (Ghoneim et al., 2008).

5.3.5 Squamous Cell Carcinoma

The high frequency of SCC is one of the main distinctive features of carcinoma in the SABC and has been noted for a long time in different reports from Egypt, A relative frequency of 59% was recently reported (Ghoneim et al., 1997, 2008). This contrasts sharply with the relative infrequency of true squamous cell carcinoma in the Western world, which varied between 3% and 7% (El-Bolkainy et al., 1981b). The predominance of SCC in SACB series is probably related to squamous metaplasia and dysplasia which are relatively common in chronic Schistosomal cystitis that are frequently associated (65%) with this type of carcinoma (Khafagy et al.,1972). Fibrosis of the bladder wall of schistosomal origin has long been suspected as a limiting factor against tumor spread. Tissue reactions to schistosome eggs in the bladder wall, pelvic lymphatics, and regional lymph nodes were proposed as limiting factors against neoplastic spread. However the limited tendency of lymphatic spread of advanced tumors in schistosomal patients was explained by others as caused by predominance of low grade tumors in these patients (El-Bolkainy et al., 1981b). Histologically, SCC is composed of one cell type exhibiting squamous differentiation throughout the tumor. Malignant squamous cells may exhibit one or more of the following features according to their grade: eosinophilic cytoplasm, sharp cell borders, intercellular bridges, and concentric cellular formations of cell nests (squamous pearls). In bilharzial series, one half of cases are grade 1 or low grade with numerous cell nests and only slight nuclear anaplasia

5.3.6 Verrucous carcinoma

This rare variant of SCC, which has only been reported to occur in the *schistosomal* bladder, (Figure 4) is characterized by a low-grade malignancy and absence of lymph node or distant spread. It contributing 4.6% of SCC or 3.4% of all types of SABC (El-sebai, 1978)).

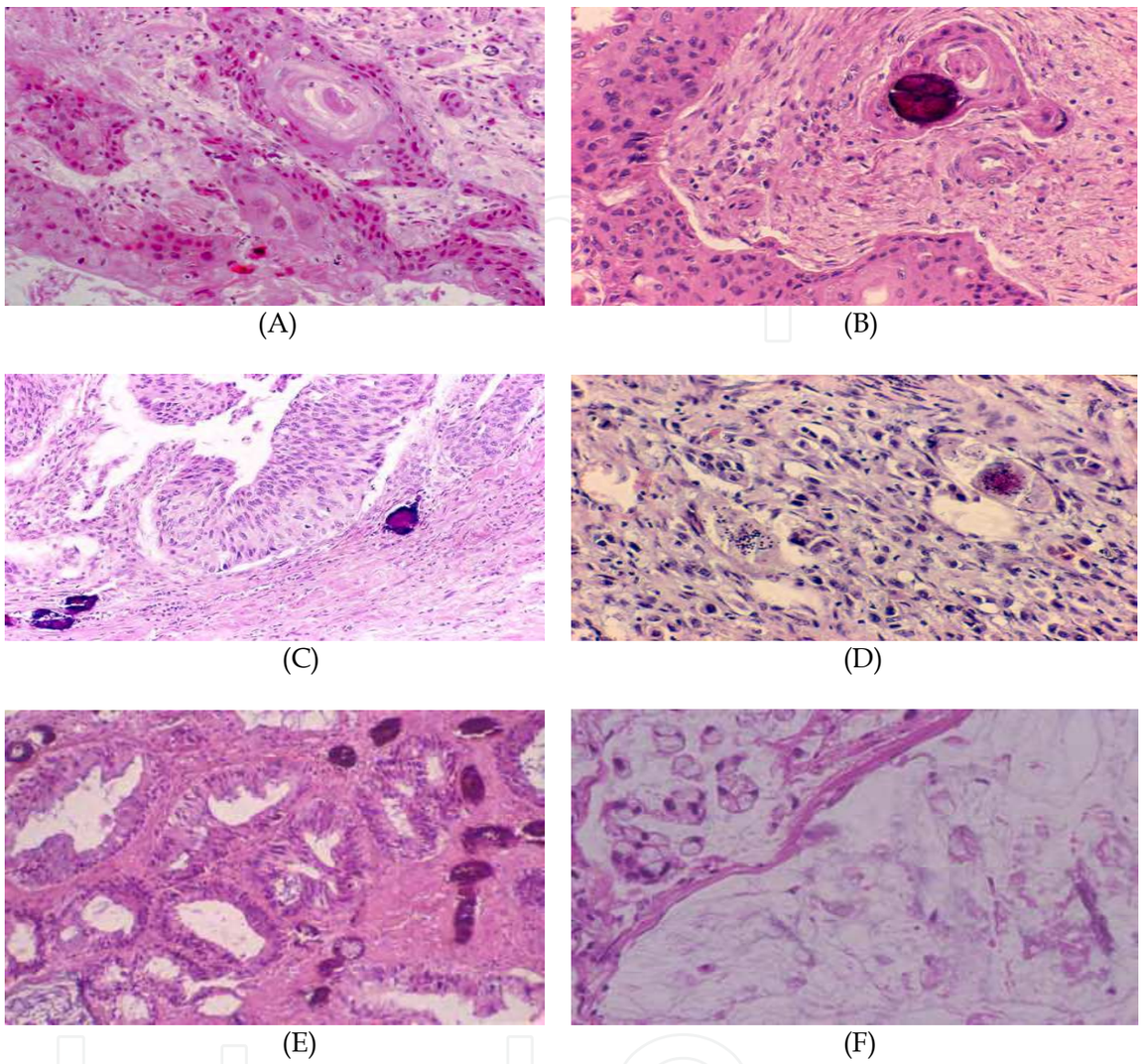


Fig. 3. A) Squamous cell carcinoma. B) Squamous cell carcinoma, urinary bladder. Notice the Schistosoma ova. C) Transitional cell carcinoma. D) Transitional cell carcinoma, Notice the vaible Schistosoma ova. E) Adenocarcinoma intestinal type. F) Mucinous adenocarcinoma

Verrucous carcinomas are divided into pure form which is exceptionally rare, and verrucous carcinoma associated with an invasive component (verrucoid carcinoma) which is more common. The former is a tumor of low malignant potential, but the latter will rather behave as conventional squamous cell carcinoma. Histologically, the tumor is a well differentiated, hyperkeratotic squamous cell carcinoma with elongated surface projections and down growths of club-shaped finger-like processes. The deeply advancing margin has a pushing rather than infiltrating border, where the cells are arranged in large bulbous masses of cohesive squamous cells.

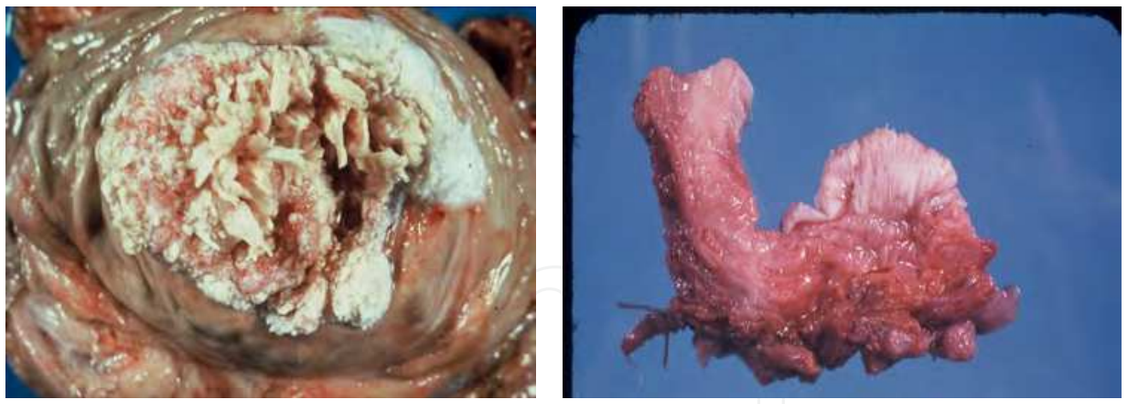


Fig. 4. SABC verrucous carcinoma cystectomy & cut section. Courtesy El-Bolkainy

5.3.7 Rare variants

The decline in the prevalence of *Schistosomiasis* in Egypt during the past two decades was associated with significant changes in the pathology of bladder carcinoma. This was confirmed by a time trend analysis study which demonstrated a significant decrease in Schistosoma eggs in tissues, a decline in the relative frequency of squamous carcinoma and an increase of transitional carcinoma (Zaghloul et al., 2008). Ten unusual variants of urothelial carcinomas are recognized (Mostofi et al.,1975), namely: urothelial carcinoma with squamous or glandular metaplasia, urothelial carcinoma with lymphocytic infiltrate (lymphoepithelioma), urothelial carcinoma clear cell type, urothelial carcinoma with ectopic placental glycoprotein production, plasmacytoid variant, lipid cell variant, micropapillary variant nested or deceptively benign variant, microcystic variant and osteoclastic variant.

5.3.8 Adenocarcinoma

Primary adenocarcinoma arises on top of cystitis glandularis, and is a rare tumor in western literature with a reported incidence of about 2%. This tumor type is more frequently encountered in areas where Schistosomiasis is endemic with a reported frequency variable between 6% (El-Bolkainy et al., 1981a) and 11% (Ghoneim et al.,1997). In a series of 185 patients of Schistosoma -associated primary adenocarcinoma, (El-Mekresh et al.,1998) 32% were non-mucin producing enteric type (Figure 3), 54% with interstitial mucin production, 10% with intraluminal mucin and 4% with intracellular mucin or signet ring type.

5.3.9 Undifferentiated tumors

About 2% of bladder carcinomas are too undifferentiated to be included in any of the above-mentioned histologic types. This heterogeneous group is generally highly aggressive and associated with very poor prognosis. It includes: small cell carcinoma, spindle and giant cell carcinoma and carcinosarcoma.

6. Early detection

Current methods of investigation of bladder cancer involve cystoscopy, ultrasound scanning and contrast urography, with additional information provided by cytology. These methods, although having a high detection rate, are expensive, time-consuming, invasive and uncomfortable.

6.1 Urine cytology

Cytology of voided urine or bladder washes is the most established noninvasive method in the work-up of haematuria (the most common presentation of bladder cancer) and follow-up in patients with a history of bladder cancer and is used as an adjunct to cystoscopy. This involves microscopic identification of exfoliated tumor cells based on cytological criteria (Figure 5). El-Bolkainy and Chu (1981a) used urine cytology for selective screening of rural high –risk population from 15 villages in Nile delta in Egypt for early detection of SABC. The high-risk group included farmers aged 20 years and above, and they contributed 19% of the total rural population. The tumor yield was 2 per 1000 high-risk screened and the majority of the detected tumors were at an early stage. The method has a high specificity but relatively low sensitivity, particularly in well-differentiated bladder tumors (Carmack & Soloway 2006). A meta-analysis that included data on 18 published series with 1,255 patients reported a sensitivity of 34% and specificity of 99% respectively (Lotan et al., 2003). Several factors contribute to this poor ability of urine cytology to detect cancer cells: only a small sample of urine can be processed and only a fraction of the sample can be used for final analysis which reduces the chance of capturing tumor cells. Background cells such as erythrocytes and leukocytes also confound the cytologic technique. Furthermore, cytological criteria that differentiate between low grade tumors and reactive cells can be ambiguous. (Wiener et al., 1993)

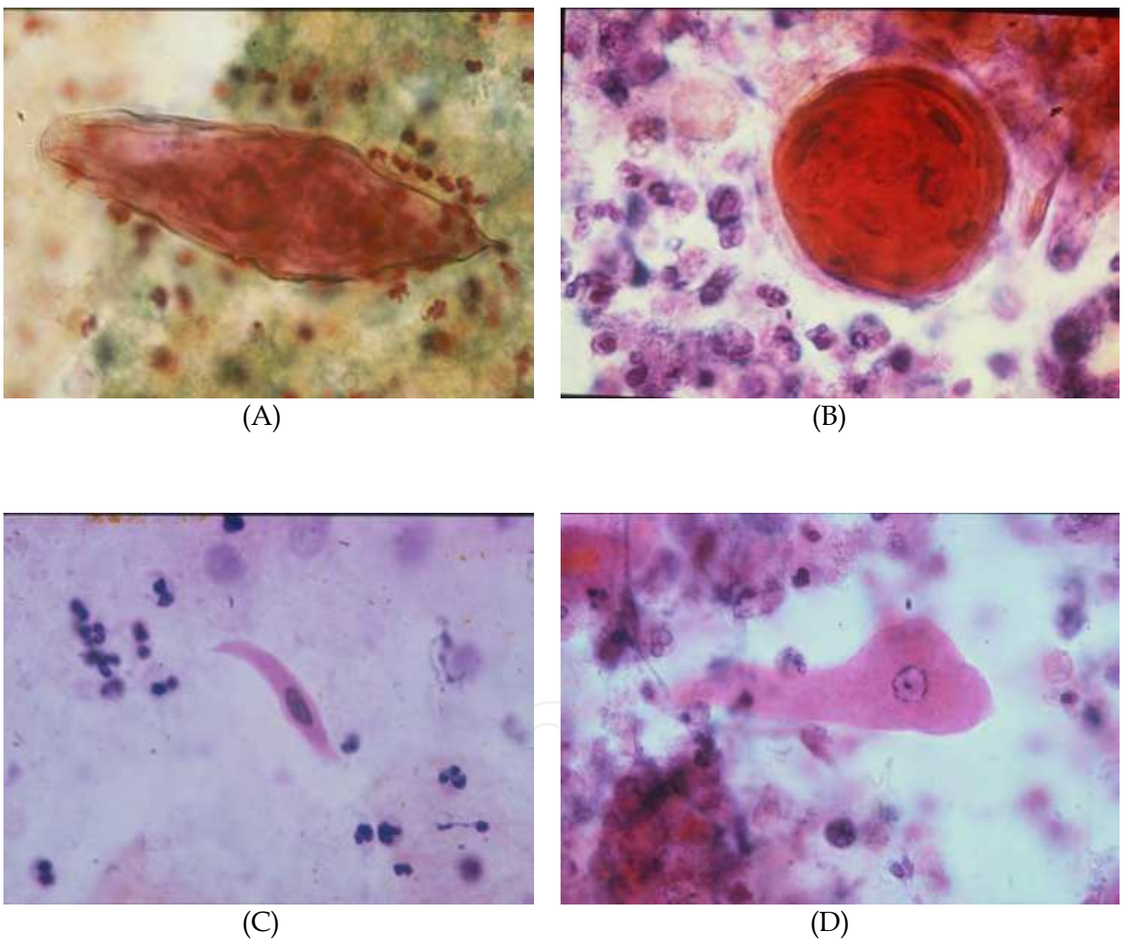
6.2 Urinary tumor markers of the bladder

The low sensitivity of urine cytology limits its use as a detection tool. Interest has been reported in identifying tumor markers in voided urine that would provide a more sensitive and objective test for tumor recurrence. Detection of bladder cancer using morphologic molecular tests could improve patient management in two ways. It would allow diagnosing tumors of the aggressive phenotype earlier and thus improve the prognosis of patients. In cases of less aggressive tumors, it could identify early disease onset and recurrences, thereby potentially reducing the need for expensive cystoscopic monitoring and surveillance procedures (Mitra et al., 2009). The following table 2 reflects the sensitivities and specificities of urine tumor markers in bladder cancer as reported in various publications

Commercially available marker	**Sensitivity (%) mean/ range**	**Specificity (%) mean/ range**
Cytology	48/ 16-89	96/ 81-100
Hematuria dipstick	68/ 40-93	68/ 51-97
BTA STAT	68/ 53-89	74/ 54-93
BTA TRAK	61/ 17-78	71/ 51-89
NMP22	75/ 32-92	75/ 51-94
NMP22 BLADDER CHEK	55.7	85.7
IMMUNOCYT	74/ 39-100	80/ 73-84
UROVYSION	77/ 73-81	98/ 96-100

Table 2. The sensitivities and specificities of selected urine tumor markers in bladder cancer (Urinary Tumor Markers for Bladder Cancer Corporate Medical Policy available at (www.bcbsnc.com)

There are several potential applications of urine tumor marker tests in patient surveillance, including: a) serial testing to detect recurrent disease earlier, b) as an adjunct to urine cytology in order to improve the detection of disease recurrence, c) providing a less expensive and more objective alternative to urine cytology, and d) directing the frequency of cystoscopy evaluation in the follow-up of patients with bladder cancer (Mitra, 2010). Currently available bladder cancer tumor markers and some of those in development are listed in Table 3,4, with an assessment of each marker and the level of evidence (LOE) for its clinical use. The LOE grading system is based on that of Hayes et al., (1996)



(A) (B)

(C) (D)

Fig. 5. A) Schistosoma ova terminal spine in urine. B) Squamous cell carcinoma, urine cytology. C) Squamous cell carcinoma spindle cell urine cytology. D) Squamous cell carcinoma tadpole, urine cytology.

Level	Type of evidence
I	Evidence from a single high-powered prospective controlled study specifically designed to test the marker, or evidence from a meta-analysis, pooled analysis or overview of level II or III studies.
II	Evidence from a study in which marker data are determined in relationship to a prospective therapeutic trial that is performed to test a therapeutic hypothesis but not specifically designed to test marker utility.
III	Evidence from large prospective studies.
IV	Evidence from small retrospective studies.
V	Evidence from small pilot studies.

Table 3. Levels of evidence (LOE) for grading clinical utility of tumor markers

Cancer Marker	LOE
BTA Stat	II
BTA Trak	II
NMP 22	II
Bladder Chek	II
Immunocyt	II
UroVysion	II
Cytokeratins 8, 18, 19	III
Telomerase – TRAP, hTert, hTR	III
BLCA-4	II
Survivin – protein and mRNA	II
Microsatellite markers	III
Hyaluronic acid / hyaluronidase	III
DD23 monoclonal antibody	II
Fibronectin	III
HCG – protein and mRNA	IV
DNA promotor regions of hypermethylated tumor suppressor and apoptosis genes	IV
Proteomic profiles (Mass spectrometry)	V

HCG, human chorionic gonadotropin; HTR, human telomerase; hTERT, human telomerase reverse transcriptase; TRAP, telomeric repeat amplification protocol; LOE, Levels of evidence(Fritsche. et al.2010)

Table 4. Currently available urine markers for bladder cancer.

6.2.1 Commercially available bladder tumor biomarkers in urine

BTA (bladder tumor antigen) stat® test, is a qualitative, point-of-care test with an immediate result that identifies a human complement factor H-related protein that was shown to be produced by several human bladder cell lines but not by other epithelial cell lines. The BTA

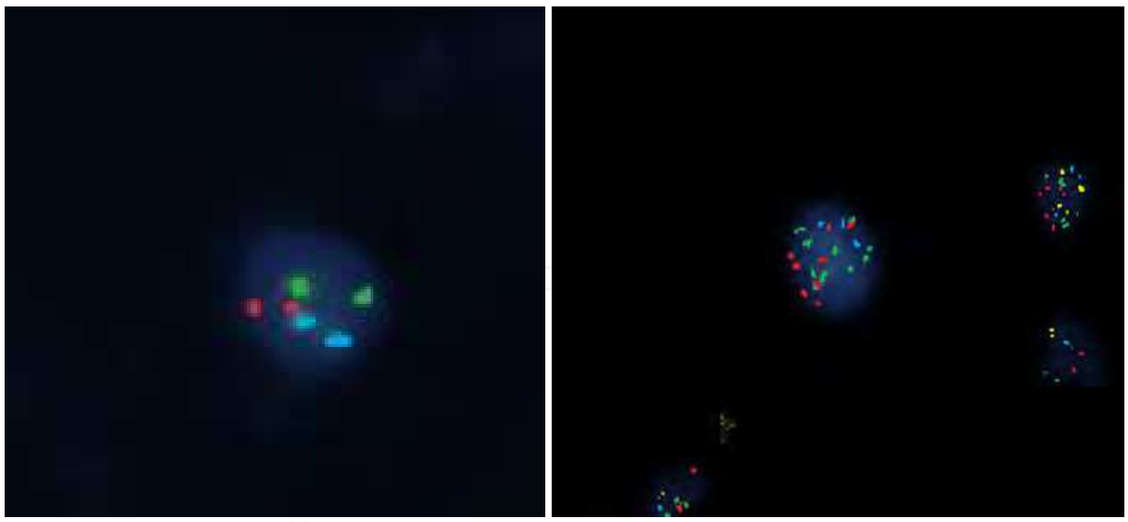
stat test is an in vitro immunoassay intended for the qualitative detection of bladder tumor associated antigen in urine of persons diagnosed with bladder cancer The BTA stat test is an in vitro immunoassay intended for the qualitative detection of bladder tumor associated antigen in urine of persons diagnosed with bladder cancer. This test is indicated for use as an aid in the diagnosis and monitoring of bladder cancer patients in conjunction with cystoscopy. **The BTA TRAK® test** provides a quantitative determination of the same protein. Both tests have sensitivities comparable to that of cytology for high-grade tumors and better than cytology for low-grade tumors. **Nuclear matrix protein 22 (NMP-22)** is a protein associated with the nuclear mitotic apparatus. It is thought that this protein is released from the nuclei of tumor cells during apoptosis. Normally, only very low levels of NMP-22 can be detected in the urine, but elevated levels may be associated with bladder cancer. NMP-22 may be detected in the urine using an immunoassay. for use in the initial diagnosis and surveillance of bladder cancer. Testing for BTA or NMP-22 has been proposed as an adjunct or alternative to urinary cytology as a technique for bladder cancer surveillance. In addition, both tests have been investigated as initial tests in patients with signs and symptoms suggestive of bladder cancer (Bas et al.,2009).

Fluorescence in situ hybridization (FISH) DNA probe technology has also been used to detect chromosomal abnormalities in voided urine to assist not only in bladder cancer surveillance but also in the initial identification of bladder cancer. fluorescence in situ hybridization (FISH) DNA probe technology is a technique to visualize nucleic acid sequences within cells by creating short sequences of fluorescently labeled, single-strand DNA, called probes, which match target sequences. The probes bind to complementary strands of DNA, allowing for identification of the location of the chromosomes targeted. The UroVysion Bladder Cancer Kit designed to detect aneuploidy for chromosomes 3, 7, 17, and loss of the 9p21 locus via in urine specimens (Figure 6). It is used as an aid for initial diagnosis of bladder cancer in patients suspicion of disease, and in conjunction with cystoscopy to monitor bladder cancer recurrence. Better performance has been reported in identification of carcinoma in situ and high grade tumors (lokeshwar et al.,2005). Another potential advantage is apparent from a study of 69 cases of bladder wash where 3 cases showed no visible mass on cystoscopy, urine cytology was negative but was positive by FISH (Badawi, 2011).

The ability of the test in detecting occult tumors that are not initially visible on cystoscopy is apparent from finding of chromosomal. (Chromosomal abnormalities detected in exfoliated cells in urine of patients under surveillance have preceded cystoscopically identifiable bladder tumors by 0.25 to 1 year in 41%-89% patients (Mitra et al., 2009). The ImmunoCyt™ testuses fluorescence immunohistochemistry with antibodies to a mucin glycoprotein and a carcinoembryonic antigen (CEA). These antigens are found on bladder tumor cells. It used mainly for monitoring bladder cancer recurrence in conjunction with cytology and cystoscopy.

6.2.2 Other urinary markers

A number of other urinary tumor markers not currently commercially available are under investigation (Steiner et al.,1997, Stein et al.,1998).The availability of many new markers for bladder cancer raises the possibility of improving the rate of cancer detection by combined use of selected markers, measured either simultaneously or sequentially (Sanchez-Carbayo et al.,2001). The objective of such panel testing should be to improve both the sensitivity and the specificity for bladder cancer detection.



(A) (B)

Fig. 6. (A) Multicolor FISH Notice absence of yellow signals denoting 9p21 deletion X1250. (B) polysomy of chromosomes 3(red signals), 7 (green signals), and 17 (aqua signals) & deletion of chromosome 9p21 (absence of yellow signals X 1000). The background shows inflammatory cells with 2 copies of each of the studied chromosomes (normal pattern). Courtesy Omnia Badawi.

7. Prognostic factors

The major challenges confronting the urologist after treatment of bladder cancer are tumor recurrence and progression. In this regard, some pathologic parameters may serve as predictors of the biologic behavior of bladder tumors. Such prognostic factors are most valuable to stratify patients and to select high-risk patients for adjuvant treatment. Transurethral resection is commonly practiced for superficial bladder carcinoma in the west, but very rarely in the SABC. In the latter, most of the patients (95.3%) present with muscle invasive carcinoma, hence radical cystectomy is the treatment of choice. (El-Sebai,1978).For this reason, we will limit our discussion here for prognostic factors for invasive tumors after radical cystectomy, of Schistosoma associated series.

7.1 Prognosis in SABC

Ghoneim and associates (2008) analyzed a large series of 2720 cases of bladder cancer in a single institution of these 2090 were men and 630 women. The average age was 43 years, which is considerably lower than in European and American series. The Median follow up was 5.5 years. *Schistosoma* eggs were found in 85% of the cystectomy specimens. Of particular interest is the histology of the tumors removed. Squamous bladder tumors were encountered in 59%, transitional cell carcinoma in 22% and adenocarcinomas (non-urachal) were seen in 11% of the cases. About 7% of the tumors were mixed or unclassified. Nodal involvement has been universally associated to a poor outcome. Regional lymph nodes were involved in 20.4%. Bilateral lymph node involvement was reported in 39.6%.There is a sentinel region which is the endopelvic region. There is no skipped metastasis. Negative nodes in the endopelvic region indicate that more proximal dissection is not necessary and bilateral endopelvic dissection is required. Lymph node positivity is a significant and independent prognostic

factor. The relative risk for the development of treatment failure among node positive patients was computed to be 1.8%. The investigators used univariate and multivariate analysis to test the following prognostic factors on disease free survival: sex, histology, stage, grade, lymph node status and presence or absence of *Schistosoma* ova. Noteworthy is that they found the same results as Bassi et al.(1999) In the multivariate analysis only tumor stage and grade as well as lymph node status had a significant impact on survival. The 5-year survival rate was 48%, also comparable to other published series (El-Mawla et al., 2001). The problem of correct clinical staging was also addressed by the authors. Clinical staging was not correct in 32% of the cases with the tendency to under stage the extent of the disease. The 5-year survival was 55% for lymph node negative patients and only 18% for patients with positive lymph nodes. Survival was strongly correlated to the stage of the disease. Stage pT3a patients 5-year survival was 43%, for pT3b it was 31% and for pT4 tumors only 8% survived 5 years and 2.6% died postoperatively These data are in concordance with data published on cystectomy series comprising transitional cell cancers (Stein et al 2001). Extended radical lymphadenectomy in treatment of SACB assures the removal of many nodal cancer deposits increases the accuracy of staging, is likely to result in improved postoperative survival (Ghoneim et al.,1979), (Leissner et al., 2004) Postoperative mortality was 2.6%. They concluded that contemporary cystectomy with continent diversion for muscle invasive disease provide minimal morbidity, offers good locoregional disease and results in acceptable quality of life (Abol-enein et al., 2004) The results published by others are remarkably similar (Stein et al., 2001, Herr et al., 2002).

7.2 Newer prognostic factors

A more sophisticated procedure may be used to evaluate the likelihood of recurrence or progression by DNA ploidy measurement, immunohistochemical staining of the basement membrane components, evaluation of cell adherence molecules, growth factors, proteases, cell surface antigens and blood group antigens, as well as by the determination of cell-cycle related proteins in bladder carcinoma (Stein et al.,1998; Grossman 1998; Zlotta & Schulman 2000,). All of these are experimental and none have reached clinical significance or become part of clinical routine. (lokeshwar et al.,2005).

8. Future prospects

SABC is theoretically a good example of a preventable malignant disease, if the parasite could be eliminated on a nationwide scale. This is far from being an easy problem. The current strategy adopted in Egypt involves a combination of snail control and mass therapy of the exposed population. Since screening projects are usually of limited nature, both in time and place, they only succeed in lowering the prevalence rate of the disease. There is still much to be learned about *Schistosomiasis* and its control. Other possibilities for bladder cancer prevention lie in smoking cessation, reduction of the occupational exposure (mainly to aromatic amines) by appropriate regulations and education activities, reduction of infection by *Schistosoma haematobium* (in endemic areas), and promotion of consumption of fruits and vegetables.

9. References

Aboul-Enein H., El-Baz M., Abdelhameed M., Abdel Latif & Ghoneim M., et al. (2004). Lymph node involvement in patients with bladder cancer treated with radical

cystectomy: A path anatomic study -A single center experience. *J Urol* 172, 5, Part 1, 1818-1821.

Al-Saleem T., Alsh N & Tawfikh L. E. (1990). Bladder cancer in Iraq: The histological subtypes and their relationship to schistosomiasis. *Ann. Saudi Med*. 10:161–164.

Al-Shukri, S. M, Alwan, H., Nayef, M. & Rahman, A. (1987). Bilharsiasis in malignant tumors of the urinary bladder. *Br. J. Urol*., 59:59–62.

Althuis MD, Dozier JD, Anderson WF, Devesa SS & Brinton LA.(2005). Global trends in breast cancer incidence and mortality 1973- 1997. *Int J Epidemiol*.; 34:405-412.

Badawi O. (2011).Evaluation of FISH for diagnosis and detection of recurrence of bladder TCC. MD thesis, PP 82-95NCI, Cairo Egypt.

Badawi A. F., Mostafa M. H.; Aboul-Asm, T. Haboubi, N. Y.; O'Connor, P. J. & D. P. Cooper. (1992). Promutagenic methylation damage in bladder DNA from patients with bladder cancer associated with schistosomiasis and from normal individuals. *Carcinogenesis* 13:877–881.

Badawi, A. F., Cooper D. P., M. H. Mostafa., M. H. Doenhoff, A. Probert, P. Fallon, R. Cooper, & P. J. O'Connor.(1993). Promutagenic methylation damage in liver DNA of mice infected with *Schistosoma* mansoni.*Carcinogenesis* 14:653–657.

Badawi, A. F., D. P. Cooper, M. H. Mostafa, T. Aboul-Asm, R. Barnard, G. P. Margison & P. J. O'Connor. (1994). *O*6-Alkylguanine-DNA-alkyltransferaseactivity in schistosomiasis associated human bladder cancer. *Eur. J. Cancer* 30:1314–1319.

Badawi, A. F.; Hirvonen, A.; Bell, D. A.; Lang, N. P. & Kadluba, F. F. (1995a). Role of aromatic amine acetyltransferases NAT1 and NAT2 in increasing carcinogen-DNA adduct formation in the human urinary bladder.*Cancer Res*. 55:5230–5237.

Badawi, A. F.; Mostafa, M. H.; Probert, A. & O'Connor, P. J.(1995b). Role of schistosomiasis in human bladder-cancer—evidence of association, etiologic factors, and basic mechanisms of carcinogenesis. *Eur. J. Cancer* Prev.4:45–49.

Badawi, AF.(1996).Molecular and genetic events in schistosomiasis associated human bladder cancer: role of oncogenes and tumor suppressor genes. *Cancer Lett*.; 105:123-138.

Bas, W.G. van Rhijn Henk G. van der Poel Theo & H. van der Kwast (2009). Cytology and Urinary Markers for the Diagnosis of Bladder *Cancer. European urology supplements* 8 536–541.

Bassi P.F. Drago Ferrantc G & Piazza N. (1999). Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. *J Urol* 161.1494-1497.

Berger, A.P. Parson, W. Stenzl, A., Steiner, H., Bartsch, G. & Klocker, H. (2002). Microsatellite alterations in human bladder cancer: detection of tumor cells in urine sediment and tumor tissue. *Eur.Urol*. 41, 532-553.

Bochner, BH., Cote, RJ., Weidner, N., et al.(1995) Angiogenesis in bladder cancer: relationship between microvessel density and tumor prognosis. *J Natl Cancer Inst*.; 87:1603-1612.

Carmack, AJ & Soloway, MS.(2006).The diagnosis and staging of bladder cancer: From RBCs to TURs. *Urology*; 67(3 Suppl 1):3-8.

Cheng 1., Chenille, I.C., Neumann, R.M. & Bostwick, D.G.(2000). Flat intraepithelial llesions of the urinary bladder cancer, 88:625-631.

Cheng 1. Cheville, lC., Neumann, R.M. & Bostwick, D.G., (1999).Natural history of urothelial dysplasia of Bladder. *Am. J. Surg. Pathol* 23:443.

Cole P, Hoover R, Friedell GH. (1972). Occupation and cancer of thelower urinary tract. *Cancer*. 29:1250-1260.

Cooper, Z Haffajee & L Taylor (1997). Human papillomavirus and schistosomiasis associated bladder cancer I Clin Pathol: *Mol Pathol*; 50:145-148.

Cote, R.J.; Dunn, M. D & Chatterjee S. J, et al. (1998). Elevated and absent pRb expression is associated with bladder cancer progression and has cooperative effects with p53. *Cancer Res*.; 58:1090-1094.

Cordon-Cardo, C.; Wartinger, D & Petrylak, D. et al.(1992) Altered expression of the retinoblastoma gene product: prognostic indicator in bladder cancer. *J Natl Cancer Inst*.; 84:1251-1256.

Coombs, LM, Piggott, DA , Sweeney, E, et al.(1991) Amplification and over-expression of c-erbB-2 in transitional cell carcinoma of the urinary bladder. *Br J Cancer.;* 63:601-608.

Czerniak, B, Deitch, D & Simmons, H, et al. (1990) Ha-ras gene codon 12 mutation and DNA ploidy in urinary bladder carcinoma. *Br J Cancer*.; 62:762-763.

Edwards BK, Ward E, Kohler BA, et al.(2010). Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer*. 116:544-573.

El Bolkainy, M.N. & Chu, E.W. (1981a).Organization of a screening project for the detection of bladder cancer, in El Bolkainy MN, Chu EW (eds): *Detection of Bladder Cancer Associated with Schistosomiasis*.Cairo, Egypt, AI-AhramPress, pp 19-28.

EI-Bolkainy, M.N., Mokhtar, N.M., Ghoneim, M.A. & Hussein, M.H.(1981b). The impact of schistosomiasis on the pathology of bladder carcinoma.*Cancer*, 48:2643-2648.

Elem, B. & Purohit, R. (1983). Carcinoma of urinary bladder in Zambia: aquantitative estimate of Schistosoma haematobium infection. *Br. J. Urol*.55:275–278.

El-Khoby T, Galal N, Fenwick A, Barakat RA, El-Hawey A & Nooman A et al (2000) The epidemiology of schistosomiasis in Egypt: summary findings in nine governorates. *Am J Trop Med Hyg* 62:88–99.

El- Merzabani, M: El-Aaser A. & Zakhary N. (1979). A study on the etiological factors of Bilharzial bladder cancer in Egypt - 1. Nitrosamines and their precursors in urine, *Europ. J. Cancer*.15: 287-291.

El-Sebai, I. (1978). Cancer of the Bilharzia bladder. *Urol. Res*. 6:233–236.

Esrig D, Elmanjian D & Groshen S, et al. (1994) Accumulation of nuclear p53 and tumorprogression in bladder cancer. *N Engl J Med*.; 331:1259-1264.

EI-Mekresh, M.M., EI-Baz., Abol-Enein, H., & Ghoneim, M.A.(1998). Primary adenocarcinoma of the urinary bladder: a report of 185 cases. *Brit. J Urol.*, 82:206-212.

El-Mawla N.G, El-Bolkainy M.N & Khaled H. M. (2001). Bladder cancer in Africa: update. *Semin Oncol*; 28:174-178.

El-Rifai, W. Kamel, D. Larramendy, ML, Shoman, S., Gad, Y., Baithun, S., El Awady, M, Eissa, S & Khaled, et al. (2000). DNA copy number changes in Schistosoma associated and non-Schistosoma-associated bladder cancer. *Am J Pathol*.; 156(3):871-878.

Falagas M.; Vassilis S; Rafailidis, P; Eleni G. Mourtzoukou, Peppas G., & Matthew E. (2010). Chronic bacterial and parasitic infections and cancer: a review *J Infect Dev Ctries;* 4(5):267-281.

Felix AS, Soliman AS & Khaled H et al. (2008) The changing patterns of bladder cancer in Egypt over the past 26 years. *Cancer Causes Control*; 19: 421–429.

Ferlay J, Shin HR, Bray F, Forman D, Mathers CD & Parkin D. (2010.) GLOBOCAN (2008) Cancer Incidence and Mortality Worldwide: *IARC Cancer Base* No. 10. Lyon, France: International Agency for Research on Cancer; Year. Available at: http://globocan.iarc.fr.

Folkman, J & Klagsbrun, M.(1987) Angiogenic factors. *Science*.; 235:442-447.

Freedman LS, Edwards BK, Ries LA & Young JL eds.(2006). Cancer Incidence inFour Member Countries (Cyprus, Egypt, Israel, and Jordan) of the Middle East Cancer Consortium(MECC) Compared with US SEER. Bethesda, MD: National Cancer Institute, : NIH Available at: http://seer.cancer. gov/publications/mecc.

Fritsche H., Grossman B., Seth P & Lerner S Ihor SawczukNACB I (2010). Practice Guidelines And Recommendations For Use Of Tumor Markers In The Clinic Bladder Cancer National Academy of Clinical Biochemistry Guidelines for the Use of Tumor Markers in Bladder Cancer 1-17 available at hfritsche@mdanderson.org.

Ghoneim, M..A., EL-Mekresh. M..M., EI-Baz, M.a., El-Attar, LA. & Ashamallah, A. (1997).Radical cystectomy for carcinoma of the bladder: critical l evaluation of the results of 1, 026 cases. *J Urol.*, 158:399.

Ghoneim, M., Abdel Latif, M., El-Mekresh, M. & Abol-Enein, H. (2008). Radical cystectomy for carcinoma of the bladder: 2, 720 consecutive cases 5 years later. *J. of urology* 180:121-127.

Grossman, H.B.; Liebert, M & Antelo M, et al.(1998); p53 and RB expression predict progression in T1 bladder cancer. *Clin Cancer Res*. 4:829-834.

Gonzalez-Zulueta M, Shibata A, Ohneseit PF, Spruck CH, III, Busch C, Shamaa M, et al. (1995).High frequency of chromosome 9p allelic loss and CDKN2 tumor suppressor gene alterations in squamous cell carcinoma of the bladder.*J Natl Cancer Inst;* 87:1383-93.

Gouda I, Mokhtar N, Bilal D, El-Bolkainy T & El-Bolkainy NM.(2007). Bilharziasis and bladder cancer: a time trend analysis of 9843 patients. *J Egypt Natl Canc Inst;* 19:158–62.

Habuchi, T., Takahashi, R., Yamada, H., Ogawa, O., Kakehi, Y., Ogura, K., Yamasaki, S., Toguchida , J., Shitake, K & Fujita, J. (1993). Influence of cigarette smoking and schistosomiasis on p53 gene mutation in urothelial cancer. *Cancer Res*. 53, 3795-3799.

Hayes, D. F., Bast, R., Desch, C. E., Fritsche, H., Kemeny, .NE & Jessup J, et al. (1996).A tumor marker utility grading system (TMUGS): A framework to evaluate clinical utility of tumor markers. *J Natl Cancer Inst*; 88:1456-1466.

Haitel A, Posch B, El-Baz M, Mokhtar AA, Susani M, Ghoneim MA & Marberger M et al (2001). Bilharzial related, organ confined, muscle invasive bladder cancer: prognostic value of apoptosis markers, proliferation markers, p53, E-cadherin, epidermal growth factor receptor and c-erbB-2.*J.Urol*; 165(5):1481-1487.

Herr, H.W.; Bochner, B. & Dalbagni, G.(2002). Impact of the number of lymphnodes retrieved on outcome in patients with muscle invasive bladder cancer. *J.Urol* 167:1295.

Hicks, R. M. (1980). Nitrosamines as possible etiological agents in Bilharzial bladder cancer. *Banbury Rep.* 12:455–471.

Hollstein, M.; Sidransky, D.; Vogelstein, B. & Harris, C. C. *(1991)*. P53 mutations in human cancers. *Science* 253:49–53.

Ibrahim, A. S. (1986). Site distribution of cancer in Egypt: twelve years experience (1970–1981), Cancer prevention in developing countries. *Pergamon Press, Oxford, UK. p.* 45–50.

Ibrahim, A. & Khaled H. (2006).Urinary Bladder Cancer. *MECC Monograph,* 97- 110.

Jemal A., Bray F., . Center M., Ferlay J, Ward E. & Forman D.(2011): Global cancer statistics *CA Cancer J Clin*; 61; 69-90.

Johansson, S. L. & Cohen, S. M.(1997). Epidemiology and etiology of bladder cancer. *Semin Surg Oncol* 13:291-298.

Jung, M. & Messing, E M. D. (2000) Molecular Mechanisms and Pathways in Bladder Cancer Development and Progression *Cancer Control*, .7 (4), 325 - 333.

Kadlubar, F. F. & Badawi, A. F. (1995).; Genetic susceptibility and carcinogen-DNA adduct formation in human urinary bladder carcinogenesis. *Toxicol Lett*. 82-83:627-632.

Kaderlik, KR. & Kadlubar, FF.(1995) Metabolic polymorphisms and carcinogen-DNA adduct formation in human populations. *Pharmacogenetics*..5:S108-S117.

Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S & Coebergh JW.*(2008)*Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. *Eur J Cancer*. 44:1345-1389.

Khaled H.M, Aly M.S & Magrath I. T.*(2000)*. Loss of Y chromosome in Bilharzial bladder cancer. *Cancer Genet Cytogenet 117:32-36.*

Khafagy, M. M.; EL-Bolkainy, M. N. & Mansour, M. A. (1972). Carcinoma of the Bilharzial bladder. A study of the associated mucosa lesions in 86 cases. *Cancer, 30: 150-159.*

Koraitim, M.M., Metwalli, N.E., Atta, MA. & El-Sadr, A.A.(1995).Changing age incidenc and pathological types of schistosoma-associated bladder carcinoma. *J Urol* 154: 1714-1716.

La Vecchia, C., B. Nagri, B. D'Avanzo, R. Savoldelli, and S. Franceshi.(1991). Genital and urinary tract diseases and bladder cancer. *Cancer Res.* 51:629–631.

Lehman, J.S. Farid, Z.; Smith, J.H.; Bassily, S & El-Masry, NA. (1973). Urinary schistosomiasis in Egypt: clinical, radiological, bacteriological and parasitological correlations. *Trans R Soc Trop Med Hyg*.67: 384-399.

Leissner J, Ghoneim M..A, Abol-Enein H, Thüroff J.W, Franzaring L, Fisch M & Schulze H, et al. (2004) Extended radical lymphadenectomy in patients with urothelial bladder cancer: results of a prospective multicenter study. *J Urol.* 171(1):139-144.

Linnenbach, A.J., Robbins, S.L., Seng B.A., Tomaszewski, J.E. Pressler, L.B & Markowitz, S.B. (1994). Urothelial carcinogenesis. *Nature* 367, 419-420.

Lokeshwar, VB., Habuchi, T., Grossman, HB, Murphy, WM., Hautmann, SH. & Hem street, GP., 3rd, et al(.2005). Bladder tumor markers beyond cytology: International Consensus Panel on bladder tumor markers. *Urology.* 66(6 Suppl 1):35-63.

Lotan, Y & Roehrborn, CG. *(2003) Sensitivity* and specificity of commonly available bladder tumor markers versus cytology: results of acomprehensive literature review and meta-analyses. *Urology*. 61(1):109- 113.

Mohkatar N. Gouda I., Adel I. (2007). Cancer pathology registry (2003-2007), 2nd edn. The National Cancer Institute at Cairo University, Cairo Egypt.

Mostafa, M. H.; Helmi, S.; Badawi, A. F.; Tricker, A. R.; Spiegelhalder, B & Preussman, R. (1994). Nitrate, nitrate and volatile N-nitroso compounds in the urine of *Schistosoma mansoni* infected patients.*Carcinogenesis*15:619–625.

Mostafa M.H, Sheweita S.A & O'Connor PJ (1999) Relationship between schistosomiasis and bladder cancer. *Clin Microbiol Rev*. 12: 97-111.

Michaud, D.S., Platz, E.A. & Giovannucci, E. (2007).Gonorrhoea and male bladder cancer in a prospective study. *Br J Cancer*; 96: 169-71.

Mitra, AP, Birkhahn, M, Penson, DF & Cote, RJ. (2009) Molecular screening for bladder cancer. Waltham, MA: UpToDate; [cited October 01, 2009.]; Available from: http://www.uptodate.com.

Mitra, AP (2010) Urine cytologic Analysis: Special Techniques for Bladder Cancer detection:*Connection* 169-177.

Mostofi, F.K. (1975). Pathology of malignant tumors of the urinary bladder. In: The Biology and. Clinical Management of Bladder Cancer. E. H. Cooper & R. E. Williams, eds., Blackwell Scientific Publications, Oxford, London, Edinburgh, Melbourne, pp. 87-109.

Osman, I, .Scher, H.I. Zhang, ZF., Pellicer, I. Hamza, R & Eissa, S.et al.(1997) Alterationsaffecting the p53 control pathway in bilharzial-related bladder cancer. *Clin Cancer Res;* 3:531-536.

Orlow, I., Lianes, P., Lacombe, L., Dalbagni, G., Reuter, V.E. & Cordon- Cardo, C. (1994). Chromosome 9 allelic losses and microsatellite alterations in human bladder tumors. *Cancer Res*. 54, 2848-2851.

O'Brien, P. J. (1988). Radical formation during the peroxidase- catalisedmetabolism of carcinogens and xenobiotics. The reactivity of these adicals with GSH, DNA and unsaturated fatty lipid. *Free RadicalBiol. Med*. 4: 216–226.

Parkin MD, Bray F, Ferlay J, Pisani P (2005) Global cancerstatistics, 2002. *Cancer J Clin* 55:74–108.

Parkin DM.(2006). The global health burden of infection-associated cancers in the year 2002. *Int J Cancer*. 118:3030-3044.

Pycha A, Mian C, Posch B, Haitel A, El Baz M & Ghoneim MA, et al.1(998). Numerical aberrations of chromosomes 7, 9 and 17 in squamous cell and transitional cell cancer of the bladder: a comparative study performed by fluorescence in situ hybridization. *J Urol*.160:737-40.; 7:1269-1274.

Reznikoff C.A., Belair C.D., Yeager T.R., Savelieva E., Blelloch R.H., Puthenveettil J.A. & Cuthill S. (1996). A molecular genetic model of human bladder cancer pathogenesis. *Semin. Oncol*. 23, 571-584.

Sanchez-Carbayo, M., Urrutia, M., Gonzalez de Buitrago, JM. & Navajo, JA..(2001) Utility of serial urinary tumor markers to individualize intervals betwecystoscopies in the monitoring of patients with bladder carcinoma. *Cancer*; 92:2820-2828.

Stein, l.P. Lieskovsky, G.Cote, R & Goshen, S.(2001). Radical cystectomy in the treatment of invasive bladder cancer: long term results in 1054 patients.*Clin Onc*. 19:2001-2006.

Stein, J. Grossfield, C & Ginsberg, D. et al. (1998) Prognostic markers in bladder cancer. A contemporary review of the literature. *J Urol*; 160:645-659.

Steiner, G, .; Schoenberg, MP & Linn, J.F., et al. (1997) Detection of bladder cancer recurrence by microsatellite analysis of urine. *Nat Med*.:3:621-624.

Sliverman D, Devesa S, Moore L & Rothman N. Bladder cancer. (2006).In: Schottenfeld D, Fraumeni FJ eds. Cancer Epidemiology and Prevention. 3rd ed. *Oxford: Oxford University Press*; :1101-1027.

Seripa, D., Parrella, P., Gallucci, M., Gravina, C., Papa, S., Fortunato, P., Alcini, A.Flammia, G., Lazzari, M. & Fazio, V.M. (2001). Sensitive detection of transitional cell carcinoma of the bladder by microsatellite analysis of cells exfoliated in urine. *Int. J. Cancer* 95, 364-369.

Simoneau A.R., Spruck C.H., Gonzalez-Zulueta M., Gonzalgo M.L., Chan M.F., Tsai Y.C., Dean M., Steven K., Horn T. & Jones P.A.(1996). Evidence for two tumor suppressor loci associated with proximal chromosome 9p to q and distal chromosome 9q in bladder cancer and the initial screening for GAS1 and PTC mutations. *Cancer Res*. 56, 5039-5043.

Tamimi, Y., Bringuier, P. P. Smit, F. Bokhoven, A. Abbas, A. Debruyne, F. M. & Schalken, J. A. (1996). Homozygous deletions of p16INK4 occur frequency in bilharziasis-associated bladder cancer. *Int. J. Cancer* 68:183–187.

Theodorescu D. (2003). Molecular pathogenesis of urothelial bladder cancer. *Histol Histopathol* 18: 259-274.

Urinary Tumor Markers for Bladder Cancer Corporate Medical Policy (2011).1 - 6 available from www.bcbsnc.com/.../medicalpolicy/urinary_tumor_markers_for_bladder.

Utting , M., Werner , W., Dahse, R., Schubert , J. & Junker, K. (2002). Microsatellite analysis of free tumor DNA in urine, serum, and plasma of patients: a minimally invasive method for the detection ofbladder cancer. *Clin. Cancer Res*. 8, 35-40.

Weintraub, M. Khaled, HM. Abdel-Rahman, Z, .Bahnasi, A. Eissa, S & Venzon, DJ. et al (1995) p53 mutations in Egyptian bladder cancer. *Int J Oncol*. 7:1269-74.

Wiener, H. G., Vooijs, G. P., van't Hof-Grootenboer, B. (1993).Accuracy of urinary cytology in the diagnosis of primary and recurrent bladder cancer. *Acta Cytol.;* 37(2):163-169.

Weiner, D.P., Koss, L.G., Sablay, B & Freed S.Z.(1997). The prevalence and significance of Brunn's nests, cystitis cystica and squamous metaplasia in normal bladders.*Vrit.J.Urol* 122:317.

Wishahi, M; Mikhail, N. E & Akl, M. (2000*)* c-erbB-2 Expresion in transitional and squamous cell carcinoma of schistosomal urinary bladder:An immunohistochemicaL and clical Study. *Egyptian Journal of* Surgery 19, (4), 255-262.

World Health Organization [homepage on the Internet]. Country Profiles, (2000) Available http://www.emro.who.int/emrinfo/index.

Xu, HJ.; Cairns P. & Hu SX, et al.(1993).Loss of RB protein expression in primary bladder cancer correlates with loss of heterozygosity at the RB locus and tumor progression. *Int J Cancer*. 53:781-784.

Yamamoto, S.; Chen, T.; Murai, T.; Mori, S.; Morimura, K. Oohara, T.Makino, S; Tatematsu, M.; Wanibuchi, H. & Fukushima, S. (1997). Geneticinstability and *p53* mutations in metastatic foci of mouse urinary bladder carcinomas induced by *N*-butyl-*N*-(4-hydroxybutyl) nitrosamine. *Carcinogenesis* 18:1877–1882.

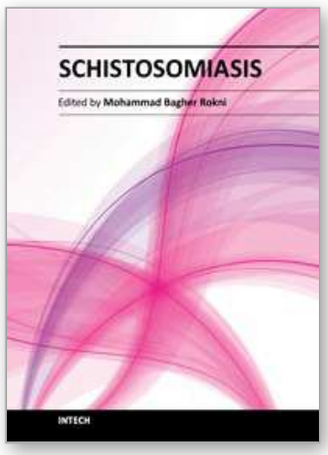
Zaghloul M, Nouh A., Moneer M; Al-Baradie M; Nazmy M & Yunis A. (2008). Time-Trend in Epidemiological and Pathological Features of Schistosoma-Associated Bladder Cancer. *Journal of the Egyptian Nat.Cancer.* 20, (2), 168-174.

Zahran, M.M., Kamel, M, Mooro, H. & Issa, A. (1976) Bilharziasis of the urinary bladder and Ureter, comparative histopathologic Study. *Urology* 8:73.

Zhang, J. Zheng, S., Fan, Z., Gao, Y., Di, X. Wang, D., Xiao, Z. Li, C., An, Q. & Cheng, S. (2001). A comparison between micro satellite analysis and cytology of urine for the detection of bladder cancer. *Cancer Lett*. 172, 55-58.

Zekri A., El-Kabany M & Khaled HM. (1995). Concordance between PCR amplifiable HPV DNA and the presence of inclusion bodies in bilharzial bladder cancer among Egyptians.*Cancer Mol Biol*; 2:441-7.

Zlotta, A & Schulman, C. (2000). Biological markers in superficial bladder tumors and their prognostic significance. *Urol Clinics of North America;* 27:179-189.



Schistosomiasis

Edited by Prof. Mohammad Bagher Rokni

ISBN 978-953-307-852-6
Hard cover, 310 pages
Publisher InTech
Published online 13, January, 2012
Published in print edition January, 2012

In the wake of the invitation by InTech, this book was written by a number of prominent researchers in the field. It is set to present a compendium of all necessary and up-to-date data to all who are interested. Schistosomiasis or blood fluke disease, also known as Bilharziasis, is a parasitic disease caused by helminths from a genus of trematodes entitled Schistosoma. It is a snail-borne trematode infection. The disease is among the Neglected Tropical Diseases, catalogued by the Global Plan to combat Neglected Tropical Diseases, 2008-2015 and is considered by the World Health Organization (WHO) to be the second most socioeconomically devastating parasitic disease, next to malaria. WHO demonstrates that schistosomiasis affects at least 200 million people worldwide, more than 700 million people live in endemic areas, and more than 200.000 deaths are reported annually. It leads to the loss of about 4.5 million disability-adjusted life years (DALYs).

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen